Letter

DOI: 10.5582/irdr.2022.01037

Differential diagnosis in Rosai-Dorfman disease: A rare case of isolated hepatic presentation mimicking a metastatic tumor with positive 18-FDG uptake

Carlo Gazia[1,*], Luca Giordano[1,2], Maria Grazia Diodoro[3], Iacopo Compalati[1,4], Riccardo Avantifiori[1,2], Gian Luca Grazi[1]

[1] Hepatopancreatobiliary Surgery, IRCCS - Regina Elena National Cancer Institute, Rome, Italy;
[2] Faculty of Pharmacy and Medicine, Department of Surgery, University of Rome "La Sapienza", Rome, Italy;
[3] Department of Pathology, IRCCS - Regina Elena National Cancer Institute, Rome, Italy;
[4] Faculty of Medicine and Psychology, Surgical and Medical Department of Translational Medicine, University of Rome "La Sapienza", Sant'Andrea Hospital of Rome, Rome, Italy.

SUMMARY Rosai-Dorfman disease (RDD) is also called sinus histiocytosis with massive lymphadenopathy, and it is caused by a histiocytic disorder with unclear etiology. It usually involves cervical lymph nodes, but it may also present with extranodal involvement. We report a rare condition of isolated hepatic RDD without nodal involvement, clinically manifested with three-month abdominal pain and tenderness of the right hypochondrium. CT- and PET-CT scans were compatible with a secondary lesion from an unknown primary tumor. Therefore, the patient underwent an atypical liver resection. Immunohistochemistry and histological results were compatible with a diagnosis of RDD. RDD is characterized by phenomena of emperipolesis, histiocytic proliferation and positive immunostaining for CD14, CD68 and S-100 protein. Cases of isolated gastrointestinal localization of RDD are particularly rare, especially in the liver. Instrumental exams might confuse RDD with other malignancies. RDD is a rare entity, which might be misdiagnosed using PET-CT due to its similarities with malignant tumors. An accurate multidisciplinary approach may help to clear diagnostic clues of this uncommon disease.

Keywords Rosai-Dorfman disease, sinus histiocytosis, liver surgery, hepatectomy

Sinus histiocytosis or non-Langerhans cell histiocytosis, also known as Rosai-Dorfman disease (RDD), represents a rare macrophage-related disorder of uncertain etiology (*1*). RDD was determined as a specific clinicopathological entity by Rosai and Dorfman in 1969 (*2*).

RDD typically develops as a localized or disseminated extranodal disease, triggering emperipolesis and histiocytic proliferation in multiple organs (*1*). It presents with fever and leukocytosis, associated with a massive and painless cervical lymphadenopathy. Immunohistochemistry (IHC) staining is often positive for S-100 protein, CD14, CD68, CD163 and negative for CD1a staining (*3*).

Gastrointestinal (GI) localizations of RDD are exceptional. A few sporadic cases with isolated hepatic involvement are reported in the literature (*3-5*). We herein describe a rare case of hepatic RDD, presenting with multiple liver nodules without nodal involvement and the role of 18-FDG PET-CT scans.

A 27-year-old Caucasian male presented with a three-month chronic nocturnal sweating and abdominal pain increasing with exertion. The patient was originally followed by another institution and dismissed with a diagnosis of liver metastasis. Nevertheless, a primary tumor could not be recognized even after a liver biopsy, which did not report any malignant cells. After being dismissed, the patient came to our attention complaining with the same symptoms. The physical examination noticed a mild tenderness of the right hypochondriac region with no other major symptoms. Laboratory tests showed C-reactive protein (CRP) levels of 21.5 mg/L. All oncological markers, including Chromogranin A tested negative. The abdominal ultrasound (US) described three hepatic nodules in VI, VIII and II-III segments (maximum diameter: 30 × 28 mm). An abdominal computed tomography (CT) with contrast was executed, showing three focal hypodense hepatic lesions, with low marginal enhancement and blurred borders, mimicking a metastatic lesion (Figure 1A). A background check on the genetic family history resulted in being

negative for chronic liver diseases, viral hepatitis and malignancies. Thus, a pancolonoscopy and a gastroscopy were performed to detect possible primary lesions, but no clues for primary gastrointestinal malignancies were identified. A contrast-enhanced US (CEUS) was performed. It showed an early and peripheral nodular contrastographic wash-out, typical of secondary lesions, also confirmed after a contrast-enhanced MR cholangiography (MRCP). Specimens from the liver nodules were collected for histological purposes. The positron emission tomography (PET)-CT scan showed an intense 18-fluorodeoxyglucose (FDG) uptake by the hepatic nodules (Figure 1B). As a consequence, an elective surgical intervention was planned. An "open approach" was chosen since the diagnosis was uncertain. The abdominal inspection was negative for suspicious malignancies, while the intraoperative US confirmed the lesions. The intraoperative extemporary pathologic exam resulted in being negative for malignant lesions and a wedge liver resection of the nodules was successfully performed (Figure 1C). The final pathologic report observed multinucleated histiocytic proliferation with emperipolesis. IHC staining detected a positive CD68 and S-100 protein with a negative CD1a. The postoperative recovery period was uneventful. The patient was successfully discharged on the VI post-operative day (POD). Three months after surgery, the patient presented at follow-up in an overall good condition.

RDD is defined as an uncommon non-Langerhans cell reactive histiocytic disorder (*2*). Globally, the prevalence of RDD accounts for one out of every 200,000 cases. The etiology of RDD is still under debate. Some studies attested to a role of viral infections from parvovirus B19, herpesvirus (HHV) and Epstein-Barr virus (EBV) (*1,5*). Other research did not endorse these results, but suggested an involvement of Kupffer cells in RDD with hepatic localization (*5*).

RDD mostly affects patients in the second and third decades of life, in otherwise good health condition with different symptoms that could mimic a lymphoma, such as a painless cervical lymphadenopathy, weight loss, night sweats, fever, neutrophilia, leukocytosis, anemia, lymphopenia and polyclonal hyperglobulinemia (*1,5*).

Histological features of RDD are emperipolesis, a massive sinusoidal dilation of large histiocytes with an abundant pale eosinophilic cytoplasm and a prominent nucleus (*1,5*). Also, RDD histiocytes test positive to CD14, CD68, CD163 and S-100 protein (*3*). Therefore, the RDD diagnosis mainly relies on histology, IHC and diagnostic imaging assessments.

Despite the fact that an RDD extranodal involvement might be encountered in more than 40% of patients with no lymphadenopathy, an intra-abdominal involvement is reported in around 4% of RDD literature cases (*3*). Gastrointestinal localizations of RDD accounts for < 1% of reported cases, representing an occasional finding,

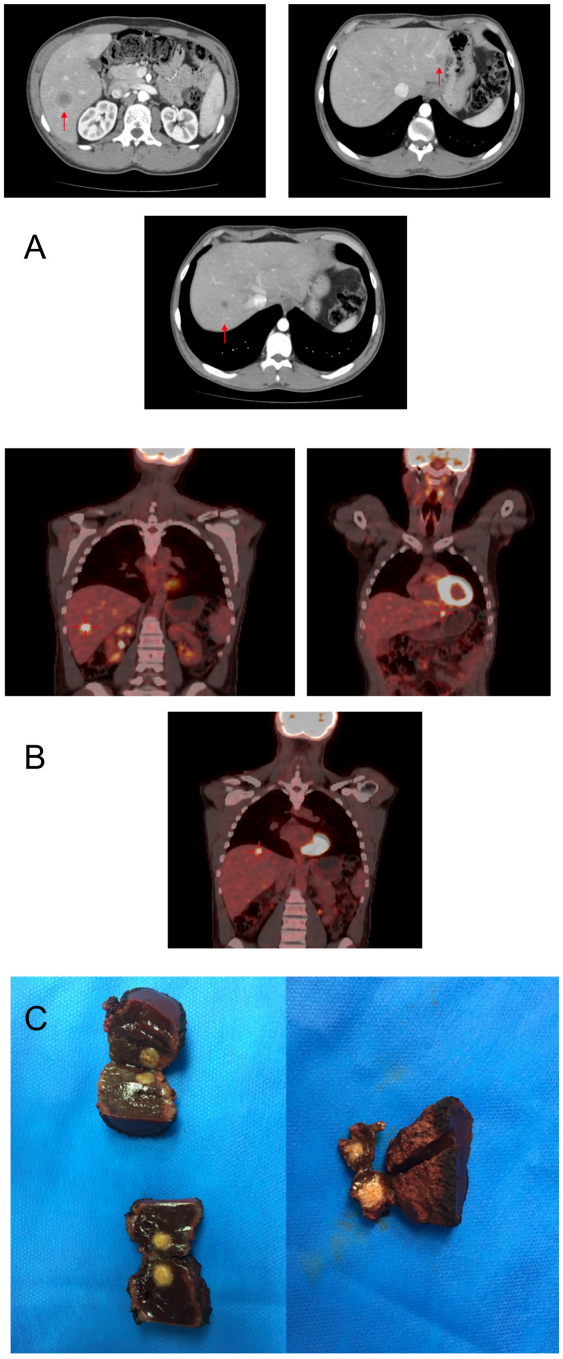

Figure 1. (A) Computed tomography (CT) scan showing an axial view of the hepatic lesions, presenting as non-enhancing hypodense nodules; (B) Hepatic nodules showing intense FDG uptake after PET-CT scans; (C) Liver parenchyma surrounding the three hepatic lesions removed.

particularly when diagnosed in liver and pancreatic tissues (*3,5*). Overall, a systemic RDD could involve the hepatic parenchyma, but reports about isolated liver lesions are extremely limited, to date (*3*).

Like other lymphoproliferative disorders, RDD lesions are FDG-avid, especially in the extranodal areas (*5,6*). Hence, despite an intense FDG uptake, which deceived an hepatic malignancy, the results of PET-CT should be carefully interpreted. In fact, in this specific

case the FDG avidity can be attributed to the intrinsic inflammatory and infiltrative component of the RDD process, and it must be remembered that a positive PET-CT is not always linked to malignant conditions (5,7). Moreover, in our case, the combination of a non-diagnostic biopsic report for tumoral cells, negative biochemical tumoral markers and the young age of the patient should have driven the diagnosis to a different etiology of pathology. On the other hand, the rarity of RDD and the absence of clear univocal guidelines concerning RDD did not facilitate its identification.

Steroids represent the first-line therapeutic option in symptomatic extensive RDD, and they are recommended with a systemic symptomatic RDD or when vital organs are threatened (*1*). In our case, a liver resection was performed to clear a diagnostic dilemma. Cases with airways, orbital and central nervous system involvement might benefit from radiotherapy, despite no clear guidelines available (*1,8*). Refractory cases to surgery and other treatments should consider chemotherapic regimens, which offer contrasting rates of success (*7,9*).

To date, this is the first young adult patient reported with multiple and solitary hepatic RDD lesions, without lymphadenopathy. The peculiarity of this case also relies on the role of PET-CT scans in RDD differential diagnosis, which could easily deceive the diagnosis of liver malignancies. Hence, according to our experience, IHC and histopathological exams are still crucial for RDD diagnosis. Clear guidelines concerning RDD are still lacking, and a multidisciplinary approach is paramount to promptly identify the correct diagnosis.

Acknowledgements

We thank all study participants for their substantial contribution to draft the present manuscript and their critical review.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Dalia S, Sagatys E, Sokol L, Kubal T. Rosai-Dorfman disease: tumor biology, clinical features, pathology, and treatment. Cancer Control. 2014; 21:322-327.
2. Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy. A newly recognized benign clinicopathological entity. Arch Pathol. 1969; 87:63-70.
3. Roosta Y, Esfahani A, Vahedi A, Tarvirizadeh K, Asoubar S, Boroofeh B, Dinparast R, Behzadi F, Raeisi M, Hosseiniazar MM. Rosai-Dorfman disease presenting with solitary liver mass without lymphadenopathy: A case report. Clin Case Rep. 2021; 9:e04709.
4. Liu C, Liu P. Extranodal Rosai Dorfman disease mimicking multiple liver metastases. Hepatobiliary Surg Nutr. 2021; 10:297-298.
5. Maheshwari A, Seth A, Choudhury M, Aggarwal V, Patra B, Aggarwal S, Mukherjee SB, Aneja S. Rosai-Dorfman disease: a case with lymphadenopathy and liver involvement. J Pediatr Hematol Oncol. 2009; 31:200-202.
6. Shaikh F, Awan O, Mohiuddin S, Farooqui S, Khan SA, McCartney W. 18F-FDG PET/CT imaging of extranodal Rosai-Dorfman disease with hepatopancreatic involvement - A pictorial and literature review. Cureus. 2015; 7:e392.
7. Foucar E, Rosai J, Dorfman R. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): review of the entity. Semin Diagn Pathol. 1990; 7:19-73.
8. Abla O, Jacobsen E, Picarsic J, *et al*. Consensus recommendations for the diagnosis and clinical management of Rosai-Dorfman-Destombes disease. Blood. 2018; 131:2877-2890.
9. Tasso M, Esquembre C, Blanco E, Moscardó C, Niveiro M, Payá A. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) treated with 2-chlorodeoxyadenosine. Pediatr Blood Cancer. 2006; 47:612-615.

Received March 6, 2022; Revised April 20, 2022; Accepted April 25, 2022.

**Address correspondence to:*
Carlo Gazia, Hepatopancreatobiliary Surgery, IRCCS Regina Elena National Cancer Institute, 00144 Rome, Italy.
E-mail: carlo.gazia@ifo.gov.it; carlo.gazia@ifo.it; carlogazia9@gmail.com

Released online in J-STAGE as advance publication April 29, 2022.